Prevalence of gastroesophageal reflux in infants with recurrent brief apneic episodes

Shahid Sheikh MD1, Thomas C Stephen MD2, Barbara Sisson MD3
Divisions of 1Pediatric Pulmonary Medicine, 2Pediatric Gastroenterology and 3Ambulatory Care, Department of Pediatrics, University of Louisville, Louisville, Kentucky, USA

BACKGROUND: Apnea in an infant can be a diagnostic dilemma for the treating pediatrician. It is suggested that in some infants, gastroesophageal reflux (GER) might be a factor in the pathogenesis of apnea, although its role as a cause of apnea is still controversial.

OBJECTIVE: To evaluate the prevalence of GER in infants presenting with recurrent brief apneic periods.

PATIENTS AND METHODS: A retrospective review of the medical records of all the infants who underwent prolonged esophageal pH studies for brief apneic episodes (n=105) at the Kosair Children’s Hospital in the six years from January 1992 to December 1997 was performed. Infants presenting with apparent life-threatening episodes were excluded.

RESULTS: Of 105 infants, 72 (68.6%) were younger than two months of age and 22 (21%) were born preterm. Fifty of 105 infants (47.6%) had positive esophageal pH studies for acid reflux. Among infants with positive pH studies, only 21 (42%) had associated gastrointestinal or feeding complaints.

CONCLUSION: GER is present in a large number of infants presenting with brief apneic episodes. Though the relationship between the two is still not fully established, GER may be a significant risk factor for such apneic episodes in infants.

Key Words: Apnea; Esophageal pH; Gastroesophageal reflux (GER); Infants

Fréquence du reflux gastro-oesophagien chez les nourrissons qui présentent de brefs épisodes récents d’apnée

CONTEXTE : Les épisodes d’apnée chez les nourrissons peuvent poser un problème diagnostique pour le pédiatre traitant. Il semblait que, chez certains enfants, le reflux gastro-œsophagien (RGO) soit un facteur de pathogenèse d’apnée, bien que ce rôle fasse encore l’objet de controverse.

OBJECTIF : Évaluer la fréquence du RGO chez les nourrissons qui présentent de brefs épisodes récents d’apnée.


RÉSULTATS : Des 105 nourrissons, 72 (68,6 %) avaient moins de deux mois et 22 (21 %) étaient nés prématurément. Dans 50 cas sur 105 (47,6 %), les analyses du pH œsophagien ont confirmé la présence de reflux acide. Parmi les enfants dont les résultats des examens se sont avérés positifs, seulement 21 (42 %) présentaient des symptômes gastro-intestinaux ou des problèmes d’allaitement associés.

CONCLUSION : Un grand nombre de nourrissons qui présentent de brefs épisodes d’apnée souffrent également de RGO. Bien que le lien entre les deux phénomènes ne soit pas clairement établi, le RGO peut s’avérer un facteur de risque important d’épisodes d’apnée chez les nourrissons.
Between 40% and 50% of infants with gastroesophageal reflux (GER) present with respiratory symptoms (1,2). The relationship of GER to respiratory problems, such as persistent wheezing and chronic cough, is well established (3-7). In infants, studies have suggested a relationship between apnea and GER (8-14), but the temporal association is still controversial (15-17). Despite the lack of conclusive evidence, apnea associated with reflux remains a common indication for fundoplication, and this approach is supported by a significant postoperative decrease in the frequency of apneic episodes (18-19). Because the resolution of GER is associated with improvement in apnea episodes, a relationship between the two is possible.

GER is not only postulated to cause obstructive apnea but is also implicated in central and mixed apnea (11,20-24). Apnea may be mediated by distal esophageal afferents and laryngospasm secondary to chemoreflexes (24-26). In a large prospective study, it was observed that some infants, who later were sudden infant death syndrome victims, had an increased number of brief apneic episodes (27), although the relationship, if any, between the two was not clear. One group reported a relationship between brief apneic episodes while sleeping and GER (28), and other groups noted a relationship between awake apnea and GER or regurgitation (11,13,15).

We undertook the present study to evaluate the prevalence of GER in infants presenting with recurrent brief apneic episodes (less than 20 s). Infants with the history suggestive of prolonged apnea (greater than 20 s) or apparent life-threatening episodes were excluded.

**PATIENTS AND METHODS**

The medical records of 105 consecutive infants with a history of recurrent brief apneic episodes, who underwent prolonged esophageal pH studies to rule out gastroesophageal reflux at the Kosair Children’s Hospital, Louisville, Kentucky between January 1992 to December 1997, were reviewed. In all infants, recurrent brief apneic episodes had been observed by the parents at home; these episodes were estimated to be less than 20 s in duration and were not associated with lirmness, cyanosis or pallor. All infants were referred for a prolonged esophageal pH study for acid reflux by eight local pediatricians. The episodes of apnea resolved either spontaneously or with minimal physical stimulation. Infants in whom apnea was associated with lirmness, cyanosis, pallor or bradycardia (suggestive of apparent life-threatening episodes) and those who required resuscitation were excluded.

Infants with the diagnosis of awake apnea had apneic episodes while awake and alert, and were either being held by the parent or were lying down. In infants who had apneic episodes while lying down, their position (supine or prone) was not documented in most cases. Infants with sleep apnea were sleeping at the time of the apneic episodes. Infants with both awake and asleep apnea had brief apneic episodes while both awake and sleeping.

Details of birth history, associated gastrointestinal symptoms (spitting, vomiting, abdominal pain, etc), age at the onset of apneic episodes, timing of the apneic episodes (awake, asleep or both), age at which prolonged esophageal pH studies were completed, history of exposure to cigarette smoking and results of esophageal pH studies were obtained from the medical records. A standard technique was used for all pH studies, using criteria described by Sondheimer (5). An esophageal antimony pH electrode was placed 3 to 4 cm above the gastroesophageal junction, and a chest roentgenogram was taken to confirm and, if necessary, adjust the position. Activity and feeding were continued as usual during the tests. All esophageal pH studies were done as an in-patient for 23 h. Before the test, the pH probe was calibrated at pH 1 and 7 to ensure accuracy. Significant acid reflux was defined as a percentage of time for which esophageal pH was below 4, of more than 6% (normal 3.4%; 95th percentile).

**Statistical methods:** For comparison between the groups, Student’s t test was used. For categorical variables, χ² analysis was used and P<0.05 was considered significant.

**RESULTS**

Prolonged esophageal pH studies were performed on 105 infants with the history of recurrent brief apneic episodes (Table 1). Of 105 infants, 72 (68.5%) were younger than two months of age at the time of esophageal pH studies. Eighty-three infants (79%) were born at term, and 22 (21%) were born preterm (less than 37 weeks of gestation). Sixty-three (60%) were males and 42 females. Fifty of 105 infants (47.6%) had positive pH studies, but none of the infants had GER. There were no statistically significant demo-
Gastroesophageal reflux in infants with brief apnea

Can Respir J Vol 6 No 5 September/October 1999 403

TABLE 2
Demographic parameters of infants with or without gastroesophageal reflux (GER)

<table>
<thead>
<tr>
<th></th>
<th>Infants with GER (n=50)</th>
<th>Infants without GER (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male to female)</td>
<td>28:22</td>
<td>35:20</td>
</tr>
<tr>
<td>Age at first episode</td>
<td>1.96±1.68</td>
<td>1.52±1.23</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at pH study (months)</td>
<td>2.98±2.73</td>
<td>2.27±2.20</td>
</tr>
<tr>
<td>Smoking exposure</td>
<td>18/42 (43%)</td>
<td>15/36 (43%)</td>
</tr>
<tr>
<td>On GER medications at the time of pH study</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Associated gastrointestinal symptoms</td>
<td>21 (42%)</td>
<td>25 (45%)</td>
</tr>
<tr>
<td>Time of apnic episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>While awake</td>
<td>32 (64%)</td>
<td>28 (51%)</td>
</tr>
<tr>
<td>While asleep</td>
<td>10 (20%)</td>
<td>20 (36%)</td>
</tr>
<tr>
<td>Both awake and asleep</td>
<td>8 (16%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born at term</td>
<td>41 (82%)</td>
<td>42 (77%)</td>
</tr>
<tr>
<td>Born preterm</td>
<td>9 (18%)</td>
<td>13 (23%)</td>
</tr>
</tbody>
</table>

Data regarding age is expressed as means ± SD

TABLE 3
Prolonged esophageal pH study parameters

<table>
<thead>
<tr>
<th></th>
<th>Infants with GER</th>
<th>Infants without GER</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of GER episodes</td>
<td>49±24.6</td>
<td>13±8.8</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Number of GER episodes longer than 5 mins</td>
<td>6.8±4.7</td>
<td>1.2±1.1</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Longest duration of GER episodes (mins)</td>
<td>43±36</td>
<td>8.4±6.4</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Period of time pH was less than 4 (mins)</td>
<td>196±113</td>
<td>32.8±18.6</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Time that pH was less than 4 (% of total time of pH study)</td>
<td>16±9.36</td>
<td>2.65±1.5</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Data is expressed as means ± SD. GER Gastroesophageal reflux

![Graph showing data](image-url)

Discussion

GER has been implicated in apnea with or without apparent life-threatening episodes (8-14,28-34). GER-induced apnea may be obstructive or central apnea (12,14,35-37). Possible mechanisms may involve stimulation of superior laryngeal nerve afferents (35,37), laryngeal and nasopharyngeal receptors (38), and reflex bradycardia (39). It has also been suggested that the esophageal pain caused by GER may trigger beta-endorphin release, which in turn decreases respiratory drive and alters chemolaryngeal reflexes (40,41). Other postulated mechanisms are vagal nerve stimulation (42), GER-induced hypoxemia (29) and anaphylaxis to milk antigens (33). Wetmore (37) has demonstrated acid-induced laryngospasm, mimicking apnea, in animals by instillation of acid into the larynx. It is, therefore, possible that exposure of the larynx area to acid present in stomach contents may stimulate the superior laryngeal nerve and trigger apnea.

In infants, airways are protected during regurgitation by anatomic closure of the upper airways at the level of the larynx, followed by the pharyngeal swallow (43). In some infants, brief respiratory pauses during swallowing may represent a secondary airway protective mechanism (14). Airway protective mechanisms during regurgitation, with or without GER, take precedence over ventilation, and, in some infants, these respiratory pauses and the airway closure following regurgitation can occasionally be prolonged and present as clinical apnea (13). An increased frequency of brief apnea is observed in infants during GER and in infants after regurgitation (13,15), suggesting that during the episodes of GER, the gastric contents may occasionally come into contact with laryngeal chemoreceptors, leading to reflex apnea, which may be variable in duration. Thus, abnormal upper airway stimuli or overactive upper airway protective reflexes may be responsible for the apneic episodes in some infants (44). Silent GER can trigger both mechanisms by introduction of passively refluxed gastric contents in the pharynx, leading to apneic events.

Brief apneic episodes can occur either while the infant is sleeping or while he or she is awake. It has been noted that many infants with awake apnea may have underlying GER, and most of these infants have obstructive apnea probably secondary to laryngospasm from gastric contents reaching the pharynx (11). Although it is postulated that apnea during sleep may be secondary to some abnormality in regulation of the control of breathing (45), it was also noted that stimulation of chemoreceptors in the proximal esophagus or larynx can result in respiratory depression (35). Recently, an association between brief apneic episodes while asleep and GER was observed (28). In our study, 32 of 60 (53%) infants with awake apnea and 10 of 30 (33%) infants with apnea while asleep had significant GER. Eight of 15 (53%) infants with both awake and asleep apnea also had significant GER. In our study, 21 (42%) infants with GER had symptoms suggestive of GER, such as frequent regurgitation and vomiting, feeding difficulties, sleeping disruptions and/or poor weight gain, along with apnea. Twenty-nine infants (58%) did not have external symptoms of GER other than apnea, suggesting that apnea may indeed be an occult manifestation of GER. Interestingly, almost the same percentage of infants without GER had similar gastrointestinal symptoms, suggesting that these symptoms may not provide adequate criteria for the diagnosis of GER.

We looked at the yield of prolonged esophageal pH studies, completed to establish a diagnosis of GER in infants presenting with brief apnea without apparent life-threatening episode. Because 47% of infants in our study had evidence of significant acid GER, it is possible that apnea may only be in-
duced by GER episodes in which gastric material reaches the chemoreceptors present in the proximal esophagus or larynx. Brief uncomplicated apneic episodes are common in infants, and we do not infer that all infants with uncomplicated brief apnea need an esophageal pH probe, and if positive, anti-reflux therapy. Although there is a high incidence of GER in infants with brief apneic episodes, this paper does not establish a temporal relationship between the two. To prove such an association, apneic episodes need to be associated with GER during prolonged esophageal pH monitoring, which was not observed in our study. Thus, while such an association will need further prospective studies, we believe that many infants presenting with recurrent brief apneic episodes may have underlying silent GER.

REFERENCES


29. Wetmore RF. Effects of the acid on the larynx of the maturing rabbit and their possible significance to the sudden infant death syndrome. Laryngoscope 1993;103:1242-54.


